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Rationally Designed Guanidine and Amidine Fungicides

John W. Liebeschuetz,* Ruth B. Katz,‡ Albert D. Duriatti§ & Mary L. Arnold

DowElanco Europe Ltd, Letcombe Regis, Wantage, Oxon OX12 9JT, UK

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Abstract: A previous investigation established that compounds containing a guanidinium or amidinium grouping are effective inhibitors of sterol Δ^8–Δ^7 isomerase and/or Δ^{14} reductase activity in plant pathogenic fungi. A binding model for known fungicidal inhibitors of this enzyme has now been used to rationally design further guanidinium or amidinium inhibitors. Three novel classes of chemistry were investigated. The results of biochemical testing against ergosterol biosynthesis in *Ustilago maydis* (DC) Corda and of in-vivo testing for fungicidal activity against *Erysiphe graminis* DC f. sp. *hordei* Marchal (powdery mildew of barley), do much to support the binding model, and compounds with significant fungicidal activity have been found.

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Key words: ergosterol biosynthesis, carbocation mimetic, fungicide, cereal pathogen

1 INTRODUCTION

Ergosterol is a component of cell membranes of certain classes of fungi. It is well established that inhibition of certain enzymatic steps in the production of ergosterol from lanosterol can be associated with fungicidal or fungistatic effects. For the control of diseases of temperate cereals, the majority of fungicides used belong to two major classes of sterol biosynthesis inhibitors (SBI). Azole fungicides, such as propiconazole and prochloraz inhibit the 14C demethylation step. These were not included in this study.

The other important class of SBI fungicides is composed of the morpholines and piperidines, principally fenpropimorph and fenpropidin. They are highly active in the control of powdery mildew (*Erysiphe graminis* DC) and have been shown to inhibit two enzymes in the sterol biosynthesis pathways of the model organisms *Saccharomyces cerevisiae* Meyer ex Hanson and *Ustilago maydis* (DC) Corda, the Δ^{14} reductase and Δ^8–Δ^7 isomerase.[1] The reaction mechanisms of both these enzymes are thought to involve a carbocation as a high energy intermediate or transition state. The morpholine/piperidine fungicides are at least partially protonated at physiological pH, and there is considerable evidence to support the hypothesis that they act by mimicking the cationic transition state of the substrate at the active site of the enzyme.[1–6] A possible mode of binding of fenpropimorph at the active site of the Δ^8–Δ^7 isomerase enzyme is shown schematically in Fig. 1.[4,7–9] The protonated nitrogen atom has been positioned over the positively charged centre of the sterol transition state. The binding to the Δ^{14} reductase enzyme may be similar, as the charge on the postulated cationic intermediate occupies a similar region in space to that in the Δ^8–Δ^7 isomerase reaction. Extensive studies aimed at optimising the activity of the morpholine/piperidine fungicides based on this model have been published.[4] Although the level of activity at the enzyme level was significantly increased, no compounds were shown to have any advantage over fenpropimorph in the field.

The consideration that the steroid carbocation is likely to be flat whereas that in fenpropimorph is probably pyramidal led us to investigate cyclic guanidines

* To whom correspondence should be addressed at: Proteus Molecular Design Ltd, Proteus House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL UK.
‡ Present address: Chiroscience Limited, Cambridge Science Park, Milton Rd, Cambridge, CB4 4WE UK.
§ Present address: 576 rue de Bernis, 30980 Langlade, France.

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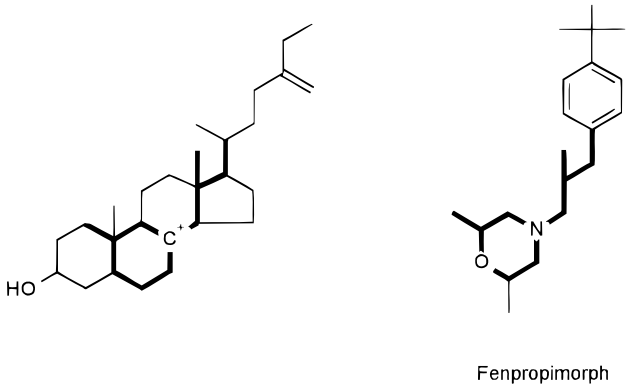


Fig. 1. Superposition of fenpropimorph over the isomerase carbocationic intermediate.

and amidines as inhibitors of the Δ^8–Δ^7 isomerase and the Δ^{14} reductase enzymes (Fig. 2).[9] Both the guanidine and the amidine functional groups, when protonated, give rise to a planar carbocation. It was hoped that this feature would lead to enhanced binding to the enzyme active site, compared with fenpropimorph. Our results in this area have been reported previously.[9] Molecules with good in-vivo fungicidal activity, and corresponding activity against ergosterol biosynthesis *in vitro* were obtained. It was shown that the structure–activity relationship (SAR) in this area closely followed that for fenpropimorph. We have now extended our investigations to three novel series of compounds to explore further the limitations of the enzyme binding models already developed.

2 DESIGN OF NOVEL STEROL BIOSYNTHESIS INHIBITORS

2.1 Hydroxypropyl guanidine and amidines

One of the most active compounds in our previously reported SAR study of the guanidine and amidine series is the amidine hydrochloride salt **2** (Fig. 2).[9] Its activity is closely matched by the corresponding guanidine salt **1**. A schematic representation of its possible action as a sterol carbocation mimic is shown in Fig. 2. This diagram shows that no account has been taken of possible interactions with the enzyme in the region occupied by ring A of the sterol. Hydrophobic interactions may exist in this region and the sterol hydroxyl group may form a hydrogen bond with some elements in the active site leading to a significant increase in the binding energy. This could be exploited to give rise to an increase in inhibitory activity at the enzyme level. One way to investigate potential binding sites normally occupied by ring A was to introduce a hydroxy propyl chain onto the structures of **1** and **2**, respectively, such that the chain could sit in the area of the binding site normally occupied by ring A of the sterol and its hydroxyl group. This concept is illustrated in Fig. 3, along with a schematic binding model. The compounds synthesised are shown in Table 1.

2.2 Cyclic 'rigid' guanidines

It has been reported previously that the gas phase 'open' conformation of fenpropimorph consistent with fitting the commonly recognised binding model in the manner of Fig. 2 is several kcal mol^{-1} above that of the lowest energy gas phase conformation.[8] A similar analysis carried out on **1** using the molecular mechanics

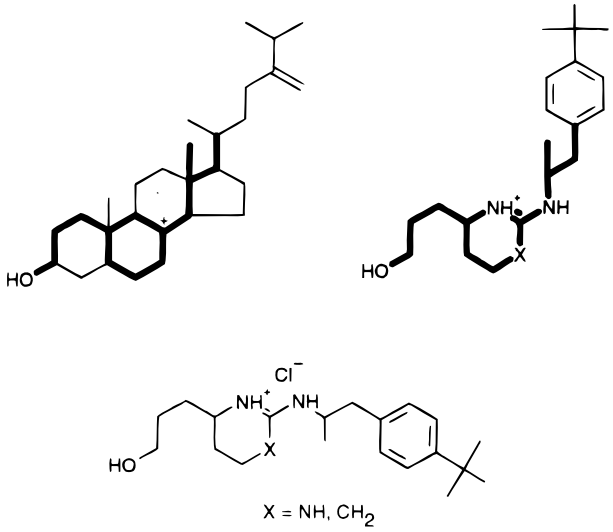
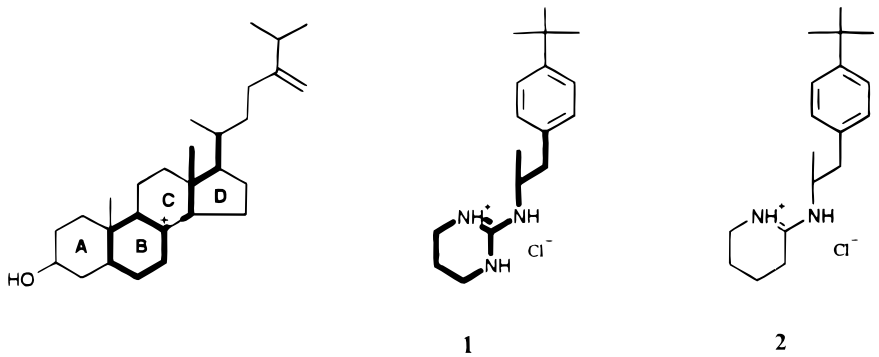


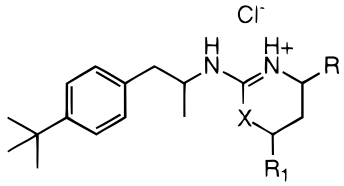
Fig. 3. Schematic representation of the binding model for hydroxypropyl guanidine and amidines.



1 **2**

Fig. 2. Schematic representation of guanidine **1** and amidine **2** in relation to the sterol cationic intermediate.

TABLE 1
Comparison of *In-vivo* and Biochemical Activity of Hydroxypropyl Compounds



5 R=$(CH_2)_3OH$ R_1=CH_3 X=NH
2 R=H R_1=H X=CH_2
6 R=$(CH_2)_3OH$ R_1=H X=CH_2

	Calculated LC_{90} (mg litre^{-1})[a]			
	E. graminis f. sp. tritici		*E. graminis f. sp. hordei*	IC_{50} (μM)[b]
	Prot.	*Erad*	*Prot.*	*U. maydis*
2	<1·56	9	6	8·6
5	<1·56	>100	27	76
6	1	8	—	3·5

[a] These compounds were compared in a 24-h test at 100, 25, 6·25 and 1·56 mg litre^{-1}.
[b] Inhibition values from the whole cell assay.

programme MM2 found that the conformation that superimposed best was 2·5 kcal mol^{-1} above the gas phase global energy minimum. The ordering of the conformations in the gas phase does not necessarily reflect their ordering in aqueous solution. Nevertheless it suggests that the free energy of binding of both fenpropimorph and **1** may be less than optimal due to the existence of a significant population of conformations which are unfavourable to binding. A common strategy used when dealing with conformationally flexible enzyme inhibitors is to construct rigid analogues that present the proposed active conformation in 'frozen' form.[10] Examination of Fig. 2 shows that the possibility exists of exploiting the binding area of ring D in the sterol for this purpose. Tying together N1 and C3 of the chain of **1** in a five-membered ring not only creates a rigid analogue but could also exploit extra hydrophobic binding in the area of the active site normally occupied by ring D.

A schematic representation of the binding model for these compounds is shown in Fig. 4. It has been shown that the stereochemistry of the 'buttressing' methyl groups of fenpropimorph[11] and **1**[9] has a considerable effect on the activity of the compound. It was therefore decided to investigate the effect on the activity of these compounds of introducing a 'buttressing' methyl group to mimic C-18 of the sterol. The superposition of a low-energy conformation of a model pyrrolinyl tetrahydropyrimidine over the postulated Δ^8–Δ^7 carbocationic intermediate is illustrated in Fig. 5, which shows two views perpendicular to each other. Both model structures were energy minimised *in vacuo* using the AM1 semi-empirical quantum chemical program.

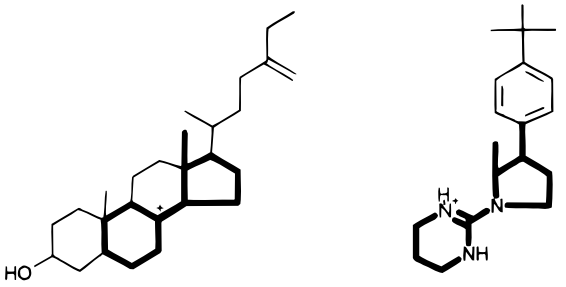


Fig. 4. Schematic representation of the binding model for the pyrrolinyl tetrahydropyrimidines.

It was also felt important to clarify the mode of action of the compounds in this series, by a limited SAR study analogous to the SAR established previously for **1** and **2**. The compounds prepared in this series are shown in Table 2.

In a related study, the effects of morpholines of type **3** and **4** (Fig. 6) were examined.[12] All four diastereromers were synthesised and tested separately. The 1*R* 3*S* isomer **3a** had in-vivo activity against *E. graminis* f. sp. *hordei* up to 20 times that of fenpropimorph.

2.3 Open-chain phenyl amidines

The final class of compounds examined here have an open-chain structure. It was envisaged that a phenyl group would mimic ring A, whilst rings B, C and D would be covered in outline. The *tert*-butylphenyl group was retained to maintain the cover of the sterol side chain. The use of a phenyl group to mimic ring A would enable a wide range of functionality to be examined and allow determination of the effects of changing the electronic nature of this part of the molecule. The binding

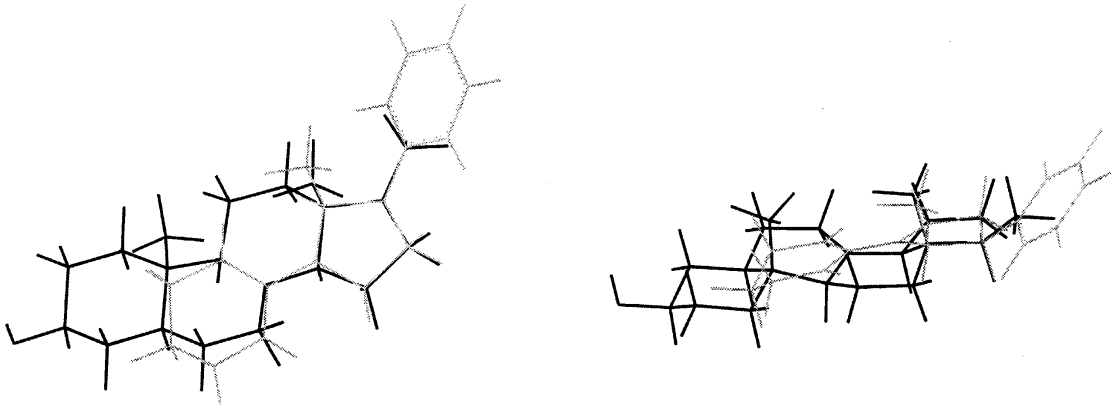
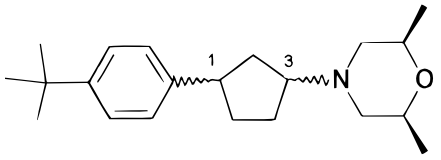


Fig. 5. Two perpendicular views of the superposition of a low-energy conformation of a model pyrrolinyl tetrahydropyrimidine over the Δ^8–Δ^7 carbocationic intermediate.

model for these compounds is shown schematically in Fig. 7. In Fig. 8 a low-energy structure for an *N*-phenyl-*N'*-phenethyl acetamidine has been fitted on the putative Δ^8–Δ^7 carbocationic sterol intermediate so that the positive centres are superimposed. Two perpendicular views, 8(a) and 8(b) are shown. Both molecules were minimised using the AM1 semi-empirical quantum chemical program. The fit is reasonable and, although the anilinyl group does not adopt the ideal conformation, it is worth observing that a polar substitution in the 4-position of the phenyl ring (here represented by



3a - 1R,3S
3b - 1S,3R
4a - 1R,3R
4b - 1S,3S

Fig. 6. Morpholine compounds investigated by Huxley-Tencer *et al.*[12]

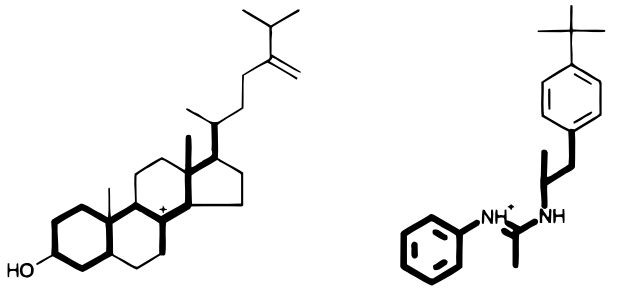
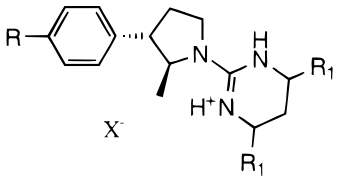
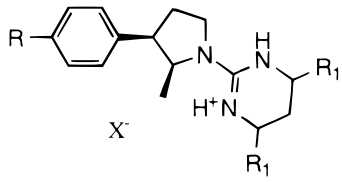


Fig. 7. Schematic binding model for open-chain phenyl amidines.

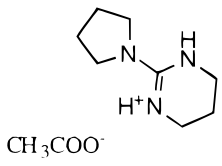
TABLE 2
Pyrrolidinyl Tetrahydropyrimidinium Compounds, 'Rigid Guanidines'



7 R=H, R_1=H, X=CH_3COO
9 R=tBu, R_1=H, X=CH_3COO
12 R=tBu, R_1=H, X=Cl
14 R=tBu, R_1=Me, X=Cl



8 R=H, R_1=H,X=CH_3COO
10 R=tBu, R_1=H, X=CH_3COO
13 R=tBu, R_1=Me, X=Cl



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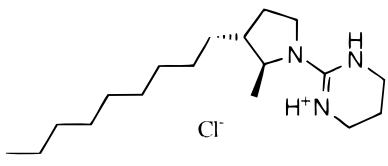

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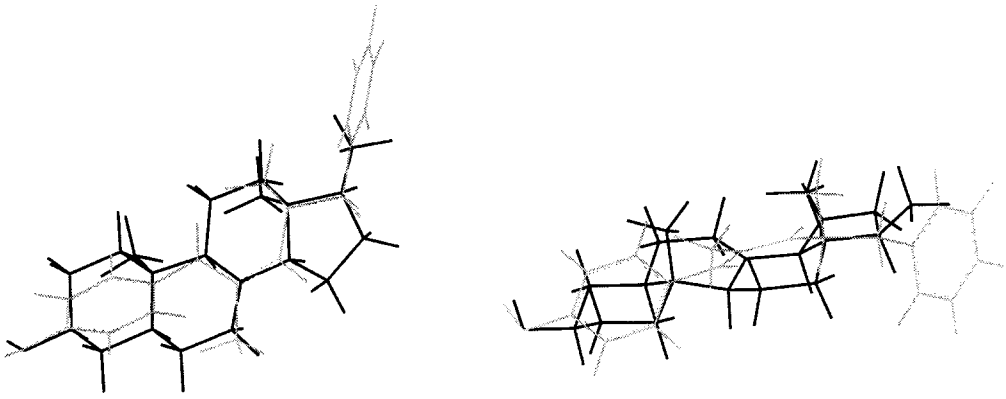


Fig. 8. Two perpendicular views of a low-energy structure for an *N*-phenyl-*N'*-phenethyl acetamidine fitted on the Δ^8–Δ^7 carbocationic intermediate.

OH) could make use of the putative polar binding site for the OH of the sterol.

3 METHODS

3.1 Synthesis of compounds

The general methods of synthesis are outlined below. Details of syntheses of individual compounds and supporting analytical data are given in the Appendix.

NMR spectra were run on a Bruker AC250 250 MHz FT spectrometer, unless otherwise stated. A Varian EM 390 NMR spectrometer was used for 90 MHz spectra. Deuterochloroform was the solvent of choice unless otherwise stated. Infra-red spectra were recorded on a Perkin-Elmer 1420 Ratio Recording spectrophotometer or on a Perkin Elmer 1760 FT spectrophotometer. Mass spectra were recorded using a Finnegan-MAT TSQ70 Triple Quadrupole mass spectrometer.

In all cases, elemental analyses are in accord with the proposed molecular formulae.

3.1.1 Synthesis of hydroxypropyl guanidine and amidine

The synthesis of the guanidine **5** is shown in Fig. 9. The β-diketone **30** was prepared by alkylation of the dianion of acetylacetone with *tert*-butyldimethylsilyl iodoethane at $-20°C$.[13]

The guanidine **31** was prepared by heating the hydrochloride salt of amine **32** with cyanamide in the absence

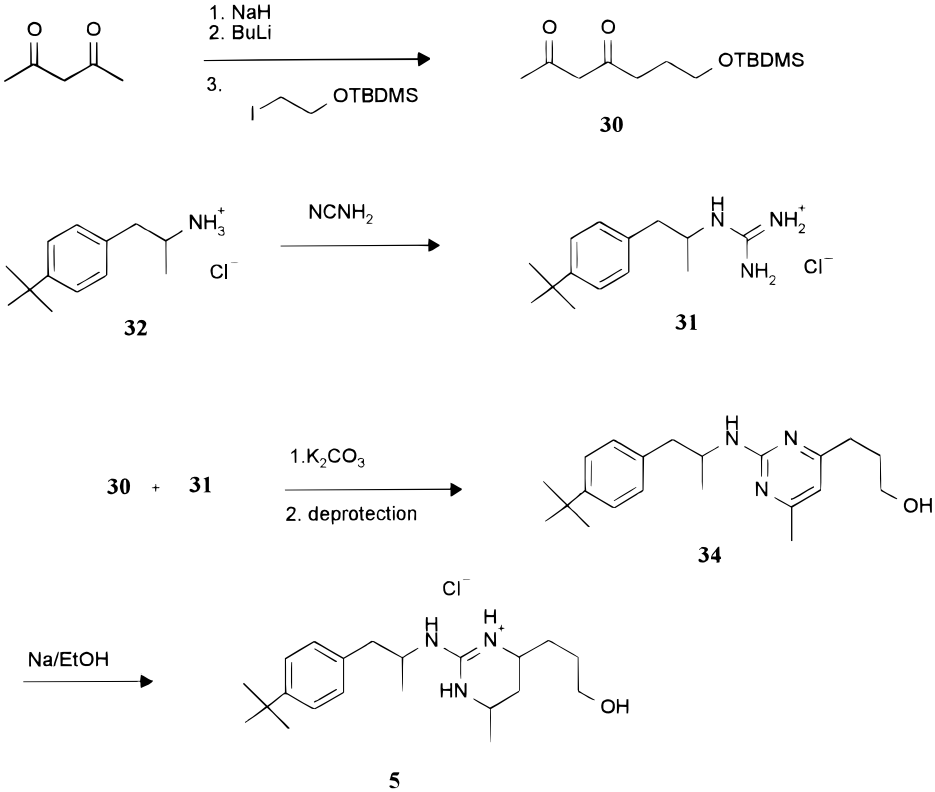


Fig. 9. Synthesis of hydroxypropyl guanidine **5**. (TBDMS = *tert*-butyldimethylsilyl).

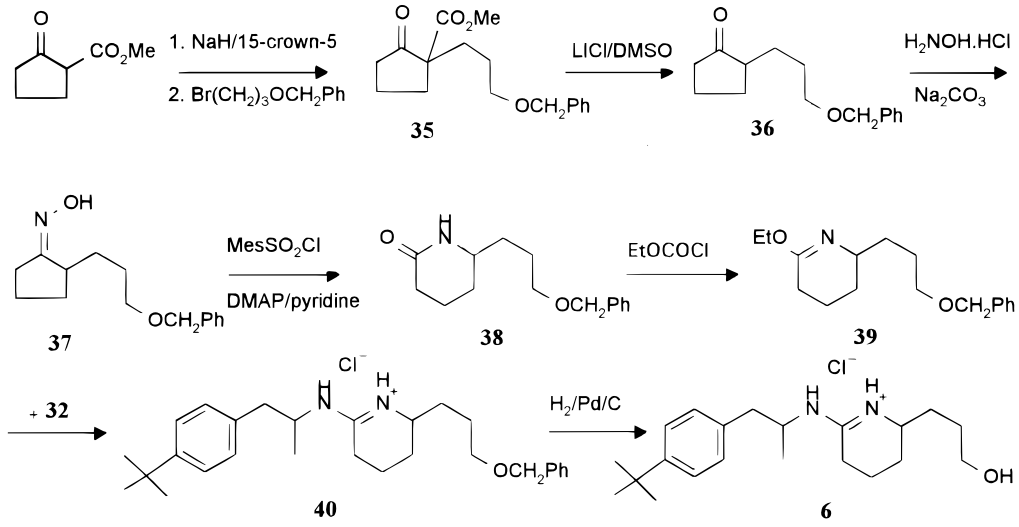


Fig. 10. Synthesis of hydroxypropyl amidine **6**. (Mes = mesityl).

of solvent. Reaction of the guanidine **31** with diketone **30** in a bomb gave the pyrimidine **33**. This was deprotected to give the hydroxypyrimidine **34** which was reduced by treatment with sodium in ethanol at reflux, giving guanidine **5** after acidic work up.

The preparation of amidine **6** is shown in Fig. 10. The anion of ethyl 2-oxocyclopentanecarboxylate was alkylated with 1-benzyloxy-3-bromopropane in the presence of 15-crown-5. Demethoxycarbonylation using lithium chloride in dimethylsulfoxide gave a cyclopentanone **36**. The oxime formation and Beckman rearrangement using mesitylene sulfonyl chloride[14] gave the lactam **38** which was obtained essentially as one isomer only.

The lactam **38** was used to prepare the amidine **40** by previously developed procedures.[9] Thus, imidate **39** was prepared, and was condensed with amine **32**. The benzyl group was removed by hydrogenation, giving amidine **6**.

3.1.2 Synthesis of rigid guanidines

Synthesis of the target guanidines required the preparation of several key 2,3-disubstituted pyrrolidines. These were prepared by the route shown in Fig. 11 (illustrated for 2-methyl-3-(4-*tert*-butylphenyl)pyrrolidine).

Wittig Horner condensation afforded the cinnamate **41** from 4-*tert*-butylbenzaldehyde. Michael addition of nitroethane to the cinnamate, followed by reduction, gave **43**. Dehydrative cyclisation under Mitsonobu conditions then afforded the desired pyrrolidine **44** as a 3 : 1 mixture of diastereomers which could not be separated.

The guanidines were prepared from the pyrrolidines *via* a two-step route previously developed for the preparation of acyclic guanidines.[9] Thus, for example (Fig. 12), **44** was condensed with 2-chloropyrimidine and the resulting aminopyrimidine was hydrogenated to afford the target cyclic guanidine.

It was found possible to separate the *cis* and *trans* diastereomeric aminopyrimidines **45** and **46** by careful flash chromatography, prior to hydrogenation. Structural assignment of the isomers was based largely on their [^{1}H]NMR characteristics. The chemical shift of the 2-methyl group differed between the isomers by 1 ppm. The most rational explanation of this is that the shift is due to shielding/deshielding by the 3-phenyl group. On this basis the isomer with the high field

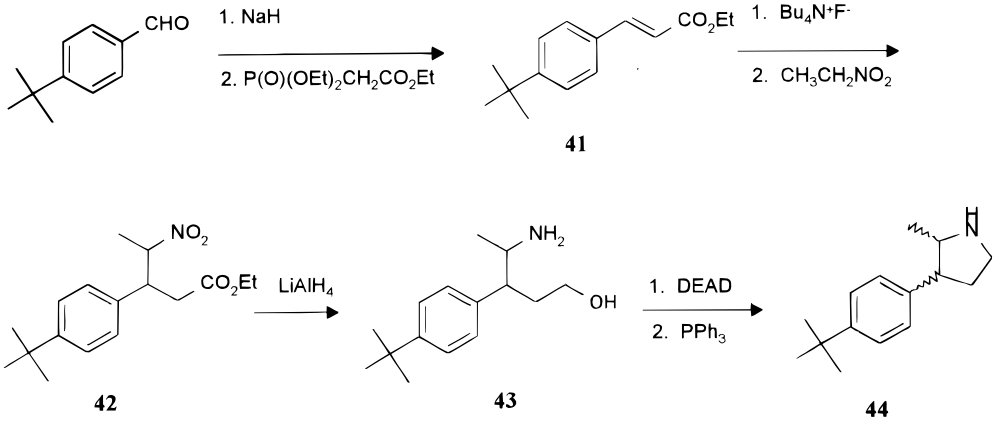


Fig. 11. Synthesis of 2,3-disubstituted pyrrolidines, key intermediates in the synthesis of the pyrrolinyl tetrahydropyrimidines. (DEAD = diethyl azodicarboxylate).

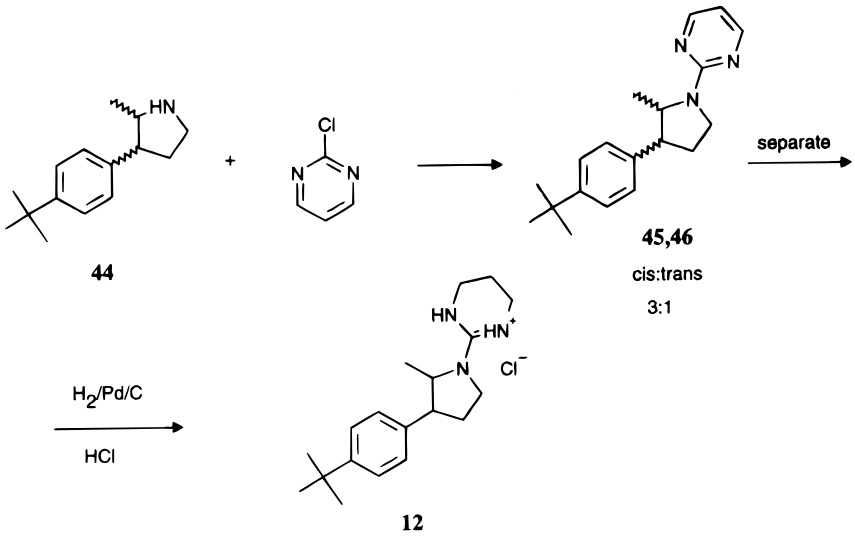


Fig. 12. Synthesis of pyrrolinyl tetrahydropyrimidines.

shifted methyl group (the major isomer) should be the *cis* isomer, having the methyl group lying above the plane of the phenyl ring and in its shielding cone; and the isomer with the low field shifted methyl group should be the minor, *trans*, isomer. Thus it was possible to make assignments for all the aminopyrimidines synthesised, including those in which the phenyl group was absent, and therefore also to establish the stereochemistry of the target guanidines.

3.1.3 Synthesis of open-chain amidines

The open-chain amidines were prepared as shown in Fig. 13. The methods used in the preparation of compound **32** have been previously reported.[9] The amine **32** was acetylated with acetyl chloride, and the resulting amide was treated with phosphorus pentachloride, followed by the appropriate aniline to give the final open-chain amidine salts. The hydroxy compounds were prepared by demethylation of the methoxy amidine salts using boron tribromide.

3.2 Biological screening methodology

3.2.1 In-vivo *methods*

Compounds were tested *in vivo* against *E. graminis* f. sp. *tritici*, (wheat powdery mildew), *E. graminis* f. sp. *hordei* (barley powdery mildew), and *Puccinia recondita* Rob. ex Desm. (wheat leaf rust). In screens for protectant activity, the plants were inoculated 24 h, or in some cases 2 h, after being sprayed. In the curative screens plants were inoculated 24 h before being sprayed. Compounds were initially tested at 400 mg litre^{-1} and, if active at this concentration, tested further at a range of lower concentrations. All active compounds in a given series were compared at a range of concentrations.

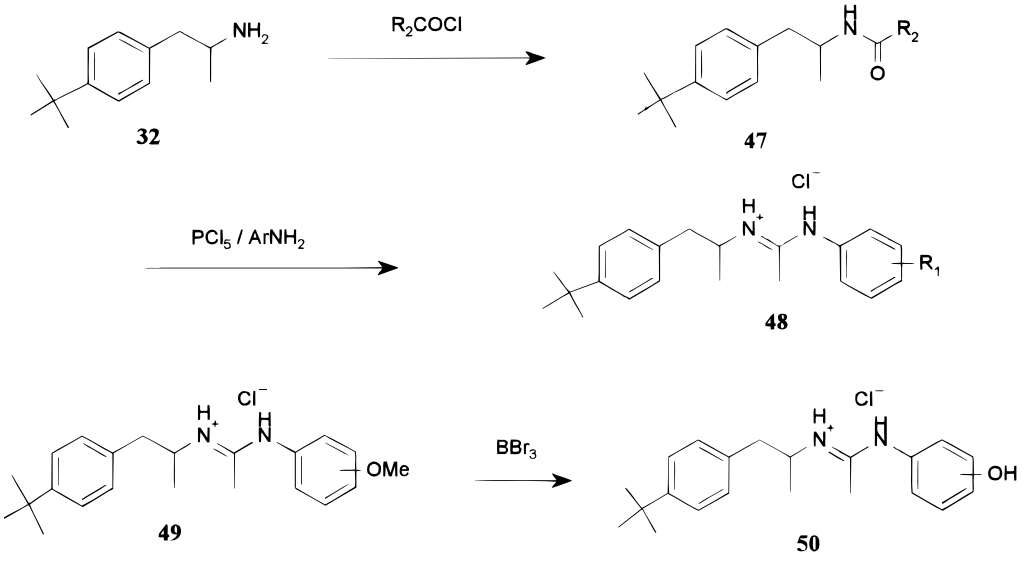


Fig. 13. Synthesis of open-chain amidines.

LC_{90} values were estimated from a plot of concentrations against bioactivity. In cases where the LC_{90} values were outside the range of concentrations used, they have been quoted as being either less or greater than the minimum or maximum concentration screened. The full experimental details have been described previously.[9]

3.2.2 In-vitro *methods*

Selected compounds were screened for activity against ergosterol biosynthesis *in vitro*. An assay using HPLC and radiolabel detection, designed to examine the constitutive sterol profile in whole cells of the smut *U. maydis* was used. Alternatively, a cell-free preparation obtained from the same organism was used. Both assays have been described previously.[9,15] In both cell-free and whole-cell assays, radiolabel incorporation into ergosterol as a proportion of incorporation into total cellular sterols was determined over a range of inhibitor concentrations. A dose/response curve of decreasing ergosterol content versus increasing concentration of inhibitor was plotted and used to determine IC_{50} values. In the main, only a single effect was detected. In general, an increase in the level of incorporation into abnormal sterol was observed concomitantly with the reduction of incorporation into the ergosterol peak.

3.3 Molecular modelling

Molecular mechanics calculations and visualisations were carried out either on a Microvax II workstation using CHEM-X software (Chemical Design Ltd) or on an Indigo Elan (Silicon Graphics Instruments) using SYBYL (Tripos Inc.).

4 RESULTS AND DISCUSSION

4.1 Hydroxypropyl compounds

Two compounds, **5** and **6**, were prepared in this series and the results of comparative testing alongside the standard **2** are shown in Table 1. While the compounds both showed good activity against *E. graminis* f. sp. *tritici* (and *E. graminis* f. sp. *hordei*), their activity was no better than that of the lead amidine **2**.

The compounds were also tested for their activity against ergosterol biosynthesis in the whole-cell assay (Table 1). Their activity was compared to that of **2**. The hydroxy propylamidine **6** showed increased efficacy over the parent amidine **2**, indicating that the hydroxy group may be favourably influencing enzyme binding. For both compounds the reduction of ergosterol levels in treated cultures was concomittant with the production of an abnormal sterol identical, in terms of retention time, with that generated by compounds **1** and **2**. This is illustrated for **6** (Fig. 14). It had previously been concluded that **1** and **2** have a similar

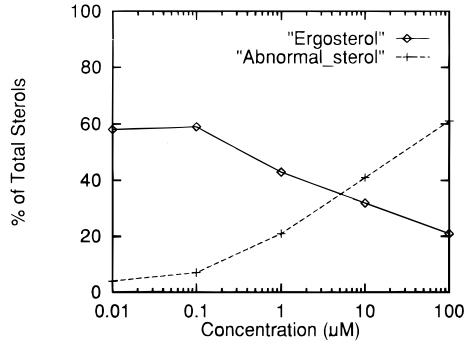


Fig. 14. Effect of hydroxypropyl amidine **6** on ergosterol biosynthesis in whole cells of *Ustilago maydis*.

mode of action to fenpropimorph, albeit only inhibiting one of the two enzymes Δ^8–Δ^7 isomerase enzyme and Δ^{14}-reductase.[9]

Despite equivalent or improved intrinsic efficacy, **6** had less in-vivo activity than **2** and this may be due to the reduced lipophilicity of these compounds, associated with the hydrophilic hydroxy group. This would perhaps decrease the mobility of the compounds in and around the plant and thus could have a negative effect on activity. It should be noted that the compounds are mixtures of diastereomers and, were these to be separated, considerable increases in activity might be observed for the individual diastereomers.

4.2 'Rigid' guanidines

The compounds prepared in this series are shown in Table 2. The majority of these compounds were screened at 400 mg litre^{-1} only and the results obtained at this rate versus *E. graminis* f. sp. *hordei* and *P. recondita* are shown in Table 3. From the model discussed earlier and from previous work in this area it could be predicted the *tert*-butylphenyl group is necessary for activity. This is confirmed by the results versus *E. gra-*

TABLE 3
In-vivo Activity of Pyrrolidinyl Tetrahydropyrimidinium Compounds

	Control at 400 mg litre^{-1} (%)[a]	
	E. graminis f. sp. hordei	*P. recondita*
7	59	NT
8	62	NT
9	83	0
10	100	0
11	0	0
12	87	66
13	52	100
14	100	0
15	79	0

[a] These data were obtained from a 24-h protectant test at 400 mg litre^{-1} only.

TABLE 4
Activity of Most Active 'Rigid Guanidines' against *Erisyphe graminis* f. sp. *hordei*

	LC_{90} (*mg litre*$^{-1}$)[a]
10	100
12	>400
14	200
15	>400

[a] These compounds were compared in a 24-h protectant test at 400, 100, 50, 25 and 10 mg litre^{-1}.

minis f. sp. *hordei* for compounds **7, 8, 11** and **15**. Of the remaining compounds, we had thought that the compounds in which the methyl group and the phenyl group were *cis* should have better activity than those where the groups were *trans*, because, according to the binding model, the groups in the natural carbocation that these superimpose are themselves *cis*. (Fig. 5). This is true in the case of **9** and **10**, **10** being the most active compound in the series (Table 3). However, it is not so in the case of compounds **13** and **14**. In the study on the cyclopentyl compounds **3a** and **b** and **4a** and **b** related to fenpropimorph and discussed earlier, this methyl group is absent, but, nevertheless, compounds with very high activities relative to fenpropimorph were obtained.[12] It is therefore possible that this methyl group does not play a significant role in the rigid guanidine series.

It is clear from Table 3 that the activities of these compounds versus *P. recondita* are different from those versus *E. graminis* f. sp. *hordei*. In this case the most active compound is **13**. Four compounds in the series were tested at lower concentrations. The activity for these compounds versus *E. graminis* f. sp. *hordei* are represented as LD_{90} values in Table 4. It can be seen that compound **10** is the most active in the series. The activity of some of these compounds at the enzyme level against ergosterol synthesis in the cell-free assay versus *U. maydis* is shown in Table 5 relative to compound **2** and fenpropimorph. The IC_{50} values are lower than the corresponding whole-cell assay results for compounds **5** and **6**. It was established previously, however, that there is generally a two orders of magnitude difference between the activities of guanidinium and amidinium

TABLE 5
Activity of 'Rigid Guanidines' against Sterol Biosynthesis in *Ustilago maydis*

	IC_{50} (μM)[a]
7	2·8
8	1·3
9	0·95
10	0·61

[a] These data were obtained from the cell-free assay.

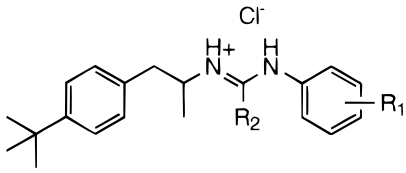
type fungicides exhibited in the two assays.[9] This was ascribed to poor cell penetration brought about by the polar nature of the highly basic guanidine and amidine moeities. Again, compound **10** is the most active in the series. The sterol profiles of cultures treated with these compounds were similar to those obtained with **1** and **2**, indicating a common mode of action. Interestingly, compound **15**, not very active *in vivo*, gave rise to a different sterol profile. At concentrations of 10 μM or more the appearance of a peak previously identified as squalene epoxide was observed, concomitant with reduction in ergosterol.[15] This suggests that this molecule may be inhibiting epoxy squalene cyclase, another enzyme thought act by a carbocationic mechanism.[16]

In conclusion it can be seen that the 'rigid' guanidines show some activity against the pathogens *E. graminis* f. sp. *hordei* and *P. recondita*. The variations in the activity in this series are consistent with the binding model. However it is clear that no compound in the series has activity in any way comparable with the lead compound in the guanidine series, compound **1**, previously shown to have an LD_{90} of the order of 10 mg litre^{-1} against these pathogens.[9]

4.3 Open-chain guanidines

The 14 compounds prepared in this series are shown in Table 6. Also shown in this table are the LC_{90} values for these compounds against *E. graminis* f. sp. *tritici* in

TABLE 6
Activity of Open Chain Guanidines against *Erisyphe graminis* f. sp. *tritici*



	R_1	R_2	LC_{90} (*mg litre*$^{-1}$)[a]
16	H	H	>400[b]
17	H	Me	40
18	2-OH	Me	>400
19	3-OH	Me	>400
20	4-OH	Me	190
21	2-MeO	Me	>400
22	3-MeO	Me	300
23	4-MeO	Me	150
24	2-Me	Me	>400
25	3-Me	Me	>400[b]
26	4-Me	Me	300
27	3-Cl	Me	>400[b]
28	4-Cl	Me	>400
29	3,4-diCl	Me	>400

[a] These compounds were compared in a 2-h protectant test at 400, 100, 25 and 6·25 mg litre^{-1}.
[b] Compound was tested at 400 mg litre^{-1} only.

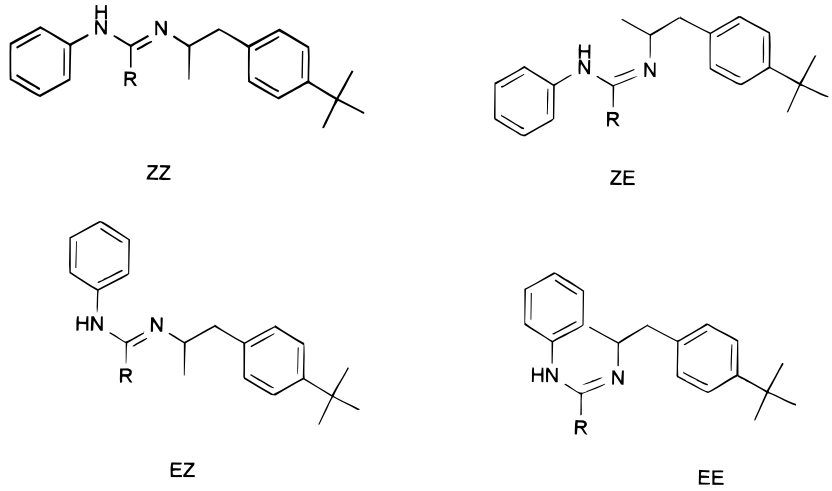


Fig. 15. The four possible geometrical isomers of the phenylacetamidines.

2-h protectant test. The model that we have proposed for the mode of action for these compounds predicts that the hydroxy compound, which can make use of the OH binding pocket, and the unsubstituted compounds are those likely to be the most active. The results shown in Table 6 are in agreement with this expectation. It is notable that the 4-OMe compound also exhibits good activity. A possible explanation is that this molecule is demethylated to the hydroxy compound *in vivo*.

It is interesting to note that the formamidine **16**, which lacks the 'buttressing' methyl group (R_2 = H) is inactive. Four geometrical isomers of the phenyl acetamidines are possible (Fig. 15). Evidence from NMR spectroscopy (Graupner, P, pers. comm.) suggests the presence of an equilibrium mixture of more than one isomer in solution. The isomer that best fits the binding model is ZE. An analysis of the relative gas phase energies of these isomers was carried out in an attempt to explain the difference in activities of the formamidine and acetamidine analogues. The molecular mechanics energy minimisation program Maximin 2, incorporating the TRIPOS force field, was used for the modelling. When R is H or Me, the EE isomer was found to be of too high an energy to be of any account. For both H or Me the ZZ and EZ isomers were found to have similar, low, energies. When R is H it was found that the ZE isomer, the proposed active isomer, was 4·3 kcal mol^{-1} in energy above that of the ZZ isomer. This is a high energy difference to be compensated for by extra enzyme binding interactions and may explain why the formamidines are only poorly active. In comparison, when R is Me, the ZE isomer has a similar energy to both the ZZ and EZ isomers. Another difference between the two cases was that for R = H, the phenyl ring was found to be planar to the amidine system in both isomers, whereas with R = Me it was pushed out of the plane. A planar phenyl group would provide a better fit for the model. It would appear, therefore, that the conformational energy argument could be the overriding effect.

Three compounds in this series were subject to further comparative tests versus *E. graminis* f. sp. *hordei* and *E. graminis* f. sp. *tritici*. The compounds were also screened in the sterol biosynthesis whole-cell assay (Table 7). The data show the hydroxy compound **20** to be most active, followed by the unsubstituted compound **17** and the methoxy compound **23**, which is the order of activity which might be expected from the

TABLE 7
In-vivo and *In-vitro* Activity of the Most Active Open-Chain Guanidines

				LC_{90} (*mg litre*$^{-1}$)		
					E. graminis f. sp. tritici	
	R_1	R_2	IC_{50} (μM)[a] *U. maydis*	*E. graminis f. sp. hordei* *Prot.*	***Prot.***	***Erad.***
17	H	Me	19·6	50	15	<1·56
20	4-OH	Me	4·91	5	15	50
23	4-MeO	Me	43·2	>100	20	>100

[a] These are data from the whole-cell assay.
[b] These compounds were compared in a 24-h protectant test and in an eradicant test at 100, 25, 6·25 and 1·56 mg litre^{-1}.

model. The whole-plant data in the three screens shown are a little more complex, which one might expect given the added complexity in in-vivo systems. The lower lipophilicity of **20** compared to **17** may account for its decreased activity in the *E. graminis* f. sp. *tritici* curative screen, where penetration into the plant is likely to be particularly important. In each case the 4-OMe compound **23** is the least active.

In conclusion, it can be seen that some members of this series exhibit moderate activity versus *E. graminis* f. sp. *hordei*, and *E. graminis* f. sp. *tritici*, although none is more active than the amidine **2**. The strong activity exhibited by the 4-OH compound is good supporting evidence for the type of binding model we propose for this class of chemistry.

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REFERENCES

1. Baloch, R. & Mercer, E. I., Inhibition of sterol Δ^8–Δ^7 isomerase and Δ^{14}-reductase by fenpropimorph, tridemorph and fenpropidin in cell-free enzyme systems from *Saccharomyces cerevisiae*. *Phytochemistry*, **26** (1987) 663–8.
2. Steel, C. C., Baloch, R., Mercer, E. I. & Baldwin, B. C., The intracellular location and physiological effects of abnormal sterols in fungi grown in the presence of morpholine and functionally related fungicides. *Pestic. Biochem. Physiol.*, **33** (1989) 101–11.
3. Rahier, A., Schmitt, P., Huss, B., Benveniste, P. & Pommer, E. H., Chemical structure–activity relationships of the inhibition of sterol biosynthesis by *N*-substituted morpholines in higher plants. *Pestic. Biochem. Physiol.*, **25** (1986) 112–24.
4. Akers, A., Ammermann, E., Buschmann, E., Gotz, N., Himmele, W., Lorenz, G., Pommer, E. H., Rentzea, C., Rohl, F., Siegel, J., Zipperer, B., Sauter, H. & Zipplies, M., Chemistry and biology of novel amine fungicides: Attempts to improve the antifungal activity of fenpropimorph. *Pestic. Sci.*, **31** (1991) 521–38.
5. Taton, M., Benveniste, P. & Rahier, A., Mechanism of inhibition of sterol biosynthesis enzymes by *N*-substituted morpholines. *Pestic. Sci.*, **21** (1987) 269–80.
6. Taton, M., Benveniste, P. & Rahier, A., *Biorganic Chemistry in Healthcare and Technology*, ed. U. K. Pandit & F. C. Alderweireldt. Plenum Press, New York, 1991, pp. 265–8.
7. Baloch, R., *PhD Thesis*, University College of Wales, Aberystwyth.
8. Jensen, J. S., Jorgensen, F. S., Klemmensen, P. D., Hacksell, U. & Petterson, I., Conformational analysis of the fungicide fenpropimorph by molecular mechanics calculations and NMR spectroscopy. *Pestic. Sci.*, **36** (1992) 309–18.
9. Arnold, M., Duriatti, A., Katz, R. B., Liebeschuetz, J. W. & Jung, M., Guanidinium and amidinium fungicides: A new class of carbocation mimetic ergosterol biosynthesis inhibitors. *Pestic. Sci.*, **44** (1995) 341–55.
10. Silverman, R. *The Organic Chemistry of Drug Design and Drug Action*. Academic Press, San Diego, 1991, pp. 83–6.
11. Pommer, E-H., Chemical structure–fungicidal activity relationships in substituted morpholines. *Pestic. Sci.*, **15** (1984) 285–95.
12. Huxley-Tencer, A., Francotte, E. & Bladocha-Moreau, M., 1(*R*)-(2,6-*cis*-dimethylmorpholino)-3(*S*)-(*p*-*tert*-butylphenyl)cyclopentane: A representative of a novel, potent class of bio-rationally designed fungicides. *Pestic Sci.*, **34** (1992) 65–74.
13. Buynak, J. D. & Rao, M. N., α-Alkylidene β-lactams. 2. A formal stereocontrolled total synthesis of $\pm$ carpetimycin A. *J. Org. Chem.*, **51** (1986) 1571–4.
14. Grieco, P. A., Flynn, D. L. & Zelle, R. E., β-Lactam antibiotics: A formal stereocontrolled total synthesis of $\pm$thienamycin. *J. Am. Chem. Soc.*, **106** (1984) 6414–17.
15. Peacock, G. A. & Goosey, M. W., Separation of fungal sterols by normal phase high performance liquid chromatography. Application to the evaluation of ergosterol biosynthesis inhibitors. *J. Chromatogr.*, **293** (1989) 293–304.
16. Duriatti, A., Bouvier-Nave, P., Benveniste, P., Schuber, F., Delprino, L., Ballliano, G. & Cattel. L., *In-vitro* inhibition of animal and higher plant 2,3-oxidosqualene-sterol cyclases by 2-aza-2,3-dihydrosqualene and derivatives, and by other ammonium-containing molecules. *Biochem. Pharm.*, **34** (1985) 2765–77.

APPENDIX

Specific compounds tested were synthesised as follows:

1-tert-*Butyldimethylsilyloxyhexane-4,6-dione*, ***30***

Sodium hydride (11 mmol) was washed with dimethoxyethane (DME), then suspended in 20 ml DME. Acetylacetone (1 ml, 10 mmol) was added dropwise at 0°C. After 30 min, the mixture was cooled to -20°C then treated dropwise with butyl lithium (4·4 ml, 11 mmol, 2·5 M in hexane). After a further 30 min, *tert*-butyl-dimethylsilyliodoethane (3·4 g, 12 mmol) was added dropwise as a solution in 5 ml of DME. The reaction was allowed to warm to room temperature and stirred for 16 h then heated at reflux for 8 h. After cooling to room temperature, the reaction was quenched with ammonium chloride solution. The aqueous phase was extracted with ether, and the combined ethereal phases dried, and concentrated. The crude product was distilled at 2 mm Hg, 150°C, giving **30** in 35% yield. δ_H 5·52 (s, 1H), 3·60 (s, 1H); 3·64 (2H, t, $J = 7$ Hz), 2·34 (2H, t, $J = 7$ Hz), 2·05 (3H, s), 1·79–1·82 (2H, m), 0·9 (9H, s), 0·0 (6H, s), MS 258 (1%, M^+) 201·1 (100), V_{max} (film) 2960, 2940, 1610, 1100 cm^{-1}.

1-[(*4*-tert-*Butylphenyl*)-*2-propyl*]*guanidine hydrochloride*, ***31***

A mixture of 1-(4-*tert*-butylphenyl)-2-propylamine hydrochloride, **32** (4·55 g, 20 mmol) and cyanamide

(1·68 g, 40 mmol) was heated to 150°C for 10 h. The mixture was cooled to room temperature, treated with hydrochloric acid (4 M) and left to dissolve over several days. The aqueous phase was extracted into chloroform. The combined organic phase was dried and concentrated, giving 5·25 g of **31** (98%). δ_H ($CDCl_3$ + NaOD) 7·70 (H, brd, J = 7 Hz), 7·20 (2H, d, J = 7 Hz), 7·10 (2H, d, J = 7 Hz), 3·70–3·80 (1H, m), 3·1 (3H, brs), 2·87 (1H, dd, J = 12, 5 Hz), 2·60 (1H, dd, J = 12, 7 Hz), 1·25 (9H, s), 1·10 (3H, d, J = 7 Hz). δ_C 20·3, 31·3, 34·3, 42·3, 50·0, 125·5, 129·0, 134·2, 149·6, 156·5. MS 234 (100%, M^+ − HCl), 147 (30). V_{max} (KBr) 3300, 3517, 2967, 1656 cm^{-1}.

N-(*1*-(*4*-tert-*Butylphenyl*)-*2*-*propyl*)-*2*-*amino*-*4*-(*3*-tert-*butyldimethylsilyloxypropyl*)-*6*-*methylpyrimidine*, ***33***

A mixture of **31** (700 mg, 2·6 mmol) and **30** was heated in a bomb at 180°C for 12 h. The mixture was cooled, dissolved in water and extracted into dichloromethane. The organic phase was dried and concentrated. The crude product was columned on silica gel eluting with ethyl acetate + hexane (10 + 90 by volume). Compound **33** (220 mg) was obtained in 40% yield. δ_H ($CDCl_3$) 7·30 (2H, d, J = 7 Hz), 7·15 (2H, d, J = 7 Hz), 6·30 (1H, s), 4·90 (1H, d, J = 7 Hz), 4·25–4·42 (1H, m), 3·65 (2H, t, J = 7 Hz), 2·87 (1H, dd, J = 12, 5 Hz), 2·62 (1H, dd, J = 12, 7 Hz), 2·58 (2H, t, J = 7 Hz), 2·25 (3H, s), 1·82–2·00 (2H, m), 1·20 (9H, s), 1·15 (3H, d, J = 7 Hz), 0·90 (9H, s), 0·01 (6H, s). MS 455 (5%, M^+), 308 (100).

N-(*1*-(*4*-tert-*Butylphenyl*)-*2*-*propyl*)-*2*-*amino*-*4*-(*3*-*hydroxypropyl*)-*6*-*methylpyrimidine* ***34***

A solution of **33** (8·3 g, 18 mmol) and hydrochloric acid (2 M, 18 ml, 36 mmol) in water (50 ml) and dioxane (100 ml) was stirred at room temperature for three days. The mixture was then basified with sodium hydroxide solution and the dioxane was evaporated. The residue was extracted into dichloromethane. The organic phase was dried and concentrated. This was columned on silica gel, eluting with ethyl acetate + hexane (20 + 80 by volume). Compound **34** (4 g) was obtained as a crystalline solid in 65% yield. δ_H ($CDCl_3$) 7·32 (2H, d, J = 7 Hz), 7·16 (2H, d, J = 7 Hz), 6·29 (1H, s), 5·27 (1H, d, J = 7 Hz), 4·60 (1H, br), 4·20–4·40 (1H, m), 3·70 (2H, t, J = 7 Hz), 2·95 (1H, dd, J = 12, 5 Hz), 2·70 (2H, t, J = 7 Hz), 2·65 (1H, dd, J = 12, 7 Hz), 2·30 (3H, s), 1·90–2·00 (2H, m), 1·30 (9H, s), 1·15 (3H, d, J = 7 Hz), δ_C. 19·9, 21·6, 30·4, 31·3, 34·3, 34·4, 42·2, 47·7, 62·0, 108·9, 125·0, 129·1, 148·8, 161·2, 167·9, 170·1. MS 342 (15%, $M^+ + H^+$), 314 (35). V_{max} 3250, 2956, 1582, 1104 cm^{-1}.

N-(*1*-(*4*-tert-*Butylphenyl*)-*2*-*propyl*)-*2*-*amino*-*4*-(*3*-*hydroxypropyl*)-*6*-*methyl*-*3*,*4*,*5*,*6*-*tetrahydropyrimidine hydrochloride*, ***5***

A solution of **34** (1·02 g, 3 mmol) in methanol under reflux was treated with sodium pellets (90 mmol) until TLC showed the reaction to be complete. The reaction was cautiously acidified with 2 M hydrochloric acid. The solvents were evaporated, the solid residue was extracted with chloroform and the organic phase concentrated. The crude product was columned on silica gel, eluting with ethanol + chloroform (5 + 95 to 15 + 85 by volume), with a trace of acetic acid. Compound **5** (990 mg) was obtained in 86% yield as a mixture of diastereomers. δ_H (MeOD + NaOD) 7·15–7·50 (6H, m, incl 7·12 (d, J = 7 Hz) and 7·42 (d, J = 7 Hz), 4·40–4·50 (1H, m), 3·85–4·00 (1H, m), 3·50–3·70 (2H, m), 3·00 (dd, J = 12, 5 Hz), 2·50–3·10 (3H, m, incl 2·80) (dd, J = 12, 7 Hz)), 1·70–2·10 (2H, m), 1·40–1·65 (2H, m), 1·05–1·40 (17H, m, incl 1·30 (d,J = 7 Hz and 1·35 (s)), MS 346 (100%, M^+ − HCl), 328 (18). V_{max} 3400–2500. (br), 1650, 1620, 1520, 800, 750 cm^{-1}.

Methyl 1-(*3*-*benzyloxypropyl*)-*2*-*oxocyclopentanecarboxylate*, ***35***

Sodium hydride (7·9 g, 0·2 mol) was washed with THF and suspended in 200 ml THF at 0°C. Methyl 2-oxocyclopentanecarboxylate (22·3 ml, 0·18 mol) was added dropwise as a solution in 30 ml THF. The reaction was stirred for 15 min, then treated with 15-crown-5 (1·79 ml, 0·9 mol), followed by 1-benzyloxy-3-bromopropane (42·3 g, 0·18 mol), added dropwise as a solution in 30 ml THF. The reaction was heated under reflux for 10 h, after which GC analysis showed essentially complete disappearance of the starting material. The reaction was quenched with ammonium chloride solution and the aqueous phase was extracted with ether. The combined ethereal phase was dried and concentrated. The crude product was distilled at 1 mm Hg, and the fraction boiling from 100 to 140°C was collected, and chromatographed on silica gel, eluting with ethyl acetate + hexane (20 + 80 by volume). Methyl 1-(3-benzyloxypropyl)-2-oxocyclopentanecarboxylate **35** was obtained (20·2 g) in 39% yield. δ_H ($CDCl_3$, 90 MHz) 7·25–7·45 (5H, m), 4·50 (2H, s), 3·70 (3H, m), 3·50 (2H, t, J = 6 Hz), 1·50–2·60 (10H, m). V_{max} (film) 2960, 2860, 1755, 1730, 1100 cm^{-1}.

2-(*3*-*Benzyloxypropyl*)*cyclopentan*-*1*-*one*, ***36***

A solution of **35** (20 g, 0·07 mol) and LiCl (9·3 g, 0·22 mol) in DMSO (250 ml) was heated under reflux for 3·5 h. GC analysis showed the reaction to be complete. The reaction was cooled, poured into water and extracted with ether + hexane (25 + 75 by volume). The combined organic phase was washed with water, dried and concentrated, giving **36** (12·95 g) in 81% yield. δ_H ($CDCl_3$, 90 MHz) 7·20–7·50 (5H, m), 4·50 (2H, s), 3·50 (2H, t, J = 6 Hz), 1·00–2·40 (11H, m). V_{max} (film) 2950, 2880, 1740, 1100 cm^{-1}.

2-(*3*-*Benzyloxypropyl*)*cyclopentan*-*1*-*one oxime*, ***37***

A solution of sodium carbonate in 20 ml water was added slowly to a solution of **36**, (1·4 g, 6 mmol), and

hydroxylamine hydrochloride (4·2 g, 60 mmol) in ethanol (15 ml) and water (40 ml). The reaction was heated under reflux for 7 h, then cooled to room temperature. The aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and concentrated, giving **37** (1·23 g) in 83% yield. The material was used in the following reaction without further purification. δ_H ($CDCl_3$, 90 MHz) 7·90 (1H, brs), 7·20–7·40 (5H, m), 4·50 (2H, s), 3·45 (2H, t, $J = 6$ Hz), 2·25–2·75 (3H, m), 1·10–2·10 (8H, m). V_{max} (film) 3300 (br), 2930, 2850, 1730, 1690 cm^{-1}.

6-(3-Benzyloxypropyl)-2-piperidinone, ***38***
A mixture of **37** (506 mg, 2 mmol), mesitylene sulfonyl chloride (875 mg, 4 mmol), *N*,*N*-dimethylaminopyridine (trace), pyridine (0·5 ml, 6 mmol), and carbon tetrachloride (15 ml) was heated at 60°C for 5 h. Thin-layer chromatography showed complete disappearance of the oxime. The reaction was treated with water, and heating was continued for a further 5 h. The carbon tetrachloride was removed by evaporation. The solution was basified with sodium hydrogen carbonate solution, then extracted with dichloromethane. The combined organic phase was dried and concentrated. The crude material was chromatographed on silica gel, eluting with methanol–chloroform mixtures. Compound **38** (198 mg) was obtained in 36% yield, essentially as one isomer only. δ_H ($CDCl_3$, 500 MHz), 7·35–7·45 (5H, m), 5·87 (14, brs), 4·51 (2H, s), 3·48 (2H, t, $J = 6$ Hz), 3·35–3·45 (1H, m), 2·20–2·45 (2H, m), 1·85–2·00 (2H, m), 1·55–1·80 (5H, m), 1·30–1·45 (1H, m). V_{max} (KBr) 3200, 2940, 1657, 1108 cm^{-1}.

6-(3-Benzyloxypropyl)-2-ethoxy-3,4,5,6-tetrahydropyridine, ***39***
A solution of **38** (3·7 g, 15 mmol) and ethyl chloroformate (1·4 ml, 15 mmol) in dichloromethane (50 ml) was heated under reflux for 20 h. The reaction was cooled to room temperature, and washed with a solution of sodium carbonate. The aqueous phase was extracted with dichloromethane. The combined organic phase was washed with brine, dried and concentrated. The crude material was distilled at 1 mm Hg, 180°C, giving **39** (1·73 g) in 42% yield. δ_H ($CDCl_3$) 7·20–7·40 (5H, m), 4·52 (2H, s), 3·90–4·20 (2H, m), 3·40–3·60 (2H, m), 3·22–3·40 (1H, m), 1·45–2·20 (10H, m), 1·25 (3H, t, $J = 7$ Hz). V_{max} (film) 2950, 2870, 1670, 1100 cm^{-1}.

N-(*1-(4-tert-Butylphenyl)-2-propyl*)-*2-amino-6-(3-benzyloxypropyl-3,4,5,6-tetrahydropyridine hydrochloride*, ***40***
A mixture of **39** (1·73 g, 6 mmol) and **32** (1·14 g, 6 mmol) was heated in a bomb at 180°C for 16 h. The reaction was cooled and the mixture was dissolved in 3 M hydrochloric acid and washed with ether. The ethereal phase was separated and the remainder was extracted into chloroform. The combined chloroform phase was washed with brine, dried and concentrated. This material was distilled at 190°C, 2 mm Hg. The residue was chromatographed on silica, eluting with ethanol in chloroform. Compound **40** (220 mg) was obtained in 8% yield. δ_H ($CDCl_3$ + NaOD) 7·20–7·40 (9H, m), 4·50 (2H, s), 4·10–4·20 (1H, m), 3·40–3·60 (2H, m), 3·20–3·35 (1H, m), 2·63 (1H, dd, $J = 13$, 7 Hz), 1·40–2·00 10H, m), 1·29 (9H, s), 1·05 (3H, d, $J = 7$ Hz). δ_C 19·7, 20·2, 26·4, 26·6, 28·7, 31·4. 34·0, 35·4, 41·6, 46·6, 55·1, 71·0, 72·7, 124·9, 125·0, 127·3, 127·6, 128·2, 129·0, 129·3, 136·1, 138·1, 155·5. MS 420 (20% $M^+ - HCl$) 329(50), 273(75), 159(82). V_{max} 3200, 2950, 1630, 760 cm^{-1}.

N-(*1-(4-tert-Butylphenyl)-2-propyl*)-*2-amino-6-(3-hydroxypropyl-3,4,5,6-tetrahydropyridine hydrochloride*, ***6***
A solution of **40** (220 mg, 0·5 mmol) in ethanol (20 ml) and hydrochloric acid (2 M, 1·5 ml) with 10% Pd/C (20 mg) was hydrogenated at 50 psi for 4 h. The mixture was filtered through celite and concentrated, giving **6** (180 mg) in 94% yield. δ_H ($CDCl_3$ + NaOD), 7·30 (2H, d, $J = 8$ Hz), 7·05 (2H, d, $J = 8$ Hz), 4·05–4·10 (1H, m), 3·50–3·80 (2H, m), 3·05–3·12 (1H, m), 2·82 (1H, dd, $J = 13$, 5 Hz), 2·73 (1H, dd, $J = 13$, 5 Hz), 1·60–2·05 (10H, m) 1·31 (9H, s), 1·04 (3H, d, $J = 7$ Hz). δ_C 19·9, 20·4, 26·8, 30·4, 31·4, 32·6, 34·3, 39·0, 41·1, 45·9, 56·1, 62·8, 125·0, 129·4, 135·3, 149·0, 156·0. MS 330 (100% $M^+ - HCl$) 285(42), 271(70). V_{max} 3392, 2961, 1656, 1456 cm^{-1}.

*Ethyl 3-(4-*tert*-butylphenyl)propenoate*, ***41***
Sodium hydride (60% in mineral oil; 2·42 g) was washed with hexane under nitrogen. Tetrahydrofuran (30 ml) was added and the mixture cooled to 0°C. Triethylphosphonoacetate (13·8 g) in THF (50 ml) was added dropwise with stirring. Half an hour after completion of the addition 4-*tert*-butylbenzaldehyde (10 g) in THF (40 ml) was added dropwise. The mixture was allowed to warm to room temperature, the solvent evaporated and the residue taken up in ethyl acetate. The solution was washed with water, dried, filtered and the solvent removed to afford **41** as an oil (12 g). δ_H (90 MHz) ($CDCl_3$) 7·64 (1H, d, $J = 16$ Hz), 7·50 (4H, s), 6·47 (1H, d, $J = 16$ Hz), 1·35 (9H, s). V_{max}, 2960, 1705, 1628, 1604, 1170 cm.

Also in this manner:

Ethyl trans-undec-2-enoate, **47** was prepared from nonanal. B.p. 105°C (1·5 mm Hg). δ_H (90 MHz) ($CDCl_3$) 6·98 (1H, dt, $J = 15$, 7 Hz), 6·82 (1H, dt, $J = 15$, 1·5 Hz), 4·22 (2H, q, $J = 7$ Hz), 2·2 (2H, m), 1·25 (15H, m), 0·88 (3H, m). V_{max} 2929 (s), 1726 (s), 1657 (s), 1467 cm^{-1}.

*Ethyl 4-nitro-3-(4-*tert*-butylphenyl)pentanoate*, ***42***
Compound **41** (6 g), nitroethane (35 ml) and 40% tetrabutylammonium hydroxide solution in methanol (6 ml) were mixed and heated at reflux under nitrogen for 3 h. The resulting mixture was poured into 10% aqueous ammonium chloride (85 ml) and this was extracted several times with ethyl acetate. The organic solution was washed three times with 10% ammonium chloride, dried, filtered and concentrated to afford **42** (4·2 g) as an oil consisting of a mixture of diastereoisomers. δ_H (90 MHz) ($CDCl_3$) 7·33 (2H, dd), 7·1 (2H, d, $J = 7{\cdot}5$ Hz), 4·83 (1H, m), 4·00 (q, $J = 6$ Hz). 3·68 (2H quin., $J = 7$ Hz), 2·71 (2H, dd), 1·61 (d, $J = 6$ Hz) 1·38 (d, $J = 6$ Hz) 1·3 (9H, s,), 1·13 (t, $J = 6$ Hz) 1·06 (t, $J = 6$ Hz). V_{max} 2970, 1740, 1555, 1366 cm^{-1}.

Also in this manner:

Ethyl 4-nitro-3-phenylpentanoate, **48** was prepared from ethyl 3-phenyl pentenoate. δ_H (90 MHz) ($CDCl_3$) 7·3 (5H, m) 4·88 (1H, m), 4·00 (2H, m), 3·70 (1H, m), 2·78 (2H, m), 1·55 (1H, d, $J = 6{\cdot}5$ Hz) 1·30 (1H, d, $J = 6{\cdot}5$ Hz) 1·07 (3H, m)

Ethyl 3-(1-nitroethyl)undecanoate, **49** was prepared from **47**. B.p. 150°C (0·2 mm Hg). δ_H (90 MHz) ($CDCl_3$) 4·75 (1H, m), 4·20 (2H, q, $J = 7$ Hz), 2·45 (2H, m), 1·43 (3H, d, $J = 6$ Hz), 1·3 (17H, m), 0·9 (3H, m). V_{max} 2931, 2859, 1741, 1557, 1466 cm^{-1}.

*3-(4-*tert*-Butylphenyl)-4-aminopentan-1-ol*, ***43***
Nitroester **42** (6·5 g) was added dropwise to lithium aluminium hydride (5 g) suspended in anhydrous diethyl ether (200 ml) under nitrogen with stirring. The mixture was heated under reflux for ten h. Water + THF (50 + 50 by volume) was added slowly dropwise with vigorous stirring until effervescence ceased. Sodium hydroxide solution (1 M) was then added dropwise until the slurry coagulated to a course sandy consistency. The mixture was filtered and the solid washed with diethyl ether. The organic fractions were combined, washed with water, dried, filtered and the solvent evaporated off at reduced pressure to afford a gum (4 g). NMR and IR spectra of the product indicated a mixture of the two possible diastereoisomers in a ratio of 2 : 1. δ_H (90 MHz) 7·25 (4H, m), 3·55 (2H, m) 3·15 (1H, m), 2·57 (1H, m), 2·05 (2H, m) 1·33 (9H, s), 1·10 (d, $J = 5$ Hz), 0·93 (d, $J = 6$ Hz). V_{max} 3349, 3280, 2932, 2876, 1603 cm^{-1}.

In a similar manner:

3-Phenyl-4-aminopentanol, **50** was prepared from **48**. δ_H (90 MHz), ($CDCl_3/D_2O$ shake) 7·3 (5H, m), 3·45 (2H, m) 3·06 (1H, m) 2·53 (1H, m) 1·95 (2H, m) 1·07 (d, $J = 6$ Hz) 0·88 (d, $J = 6$ Hz). V_{max} 3350, 3279, 2932, 2876, 1602, 1496, 1453 cm^{-1}.

3-(1-Aminoethyl)dodecanol, **51** was prepared from **49**. δ_H (90 MHz) 3·7 (2H, m) 3·35 (3H, brs) 3·1 (1H, m) 1·1—1·8 (19H, m), 1·05, (d, $J = 6$ Hz), 0·88 (3H, m).

*3-(4-*tert*-Butylphenyl)-2-methylpyrrolidine*, ***44***
Aminoalcohol **43** (4·2 g), triphenylphosphine (4·69 g) and diethyl azodicarboxylate (3·1 g) were dissolved in THF (100 ml). Two drops of glacial acetic acid were added and the solution was heated under reflux for 2 h. During this time the initially red solution became yellow. On cooling, hexane was added until precipitation started. The mixture was then cooled in the freezer and the crystalline precipitate filtered off. The solvent was removed under reduced pressure and the residue taken up in chloroform and washed with water. The organic layer was dried and concentrated and the residue vacuum distilled (130°C, 2 mm Hg) to afford a mobile oil (3 g). NMR and IR spectra of the product indicated a mixture of the two possible diastereoisomers in a ratio of 2 : 1. δ_H (250 MHz) 7·35 (2H, m), 7·14 (2H, m), 4·2 (1H, brs),3·63 (m), 3·3 (m), 1·9–2·9 (m's), 1·3 (brs, CH_3s), 0·88 (d, $J = 6$ Hz, CH_3). V_{max} 3280, 2970, 1617, 1515, 1463 cm^{-1}.

In a similar manner:

3-Phenyl-2-methyl pyrrolidine, **52** was prepared from **50**. δ_H (250 MHz) 7·2 (5H, m), 3·35 (m), 3·27 (m), 3·16 (m), 3·04 (m), 2·73 (1H, brs), 2·24 (1H, m), 1·97 (1H, m), 1·13 (d, $J = 6$ Hz), 0·72, (d, $J = 6$ Hz). V_{max} 3238, 3035, 2968, 2878, 1728, 1605, 1498, 1454 cm^{-1}.

3-Octyl-2-methyl pyrrolidine, **53** was prepared from **51**. B.p. 100°C (0·4 mm Hg), δ_H (90 MHz) ($CDCl_3$) 3·85 (1H, brs), 2·7–3·4 (3H, m), 1·9 (2H, m), 1·3 (m), 0·9 (d, $J = 6$ Hz), 0·85 (m).

Cis- *and* trans *1-(pyrimidine-2-yl)-2-methyl-3-(4-*tert*-butylphenyl)pyrrolidine*, ***45*** *and* ***46***
Substituted pyrrolidine **44** (1·4 g), 2-chloropyrimidine (0·74 g) and diisopropylethyamine (0·83 g) were mixed together in pentanol (40 ml) and heated under reflux for 6 h. The pentanol was distilled off under reduced pressure. The residue was taken up in dichloromethane, washed with water and concentrated. Column chromatography of the residue (toluene + ethyl acetate) afforded both *cis* and *trans* isomers, stereochemically pure in a 2 : 1 ratio, yield 70%.

Cis-*isomer:* **45**. δ_H (90 MHz) 8·46 (2H, d, $J = 5$ Hz), 7·4 (4H, ABq, $J = 8$ Hz), 6·52 (1H, t, $J = 5$ Hz), 4·70 (1H, quin, $J = 7$ Hz), 3·70 (3H, m), 2·35 (3H, m), 1·35 (9H, s), 0·90 (3H, d, $J = 7$ Hz). V_{max} 3420, 2970, 1584, 1544, 1513, 1477 cm^{-1}.

Trans-*isomer:* **46**. δ_H (90 MHz) 8·38 (2H, d, $J = 4{\cdot}5$ Hz), 7·26 (4H, ABq, $J = 8$ Hz), 6·50 (1H, t, $J = 4{\cdot}5$ Hz), 4·33 (1H, quin, $J = 6$ Hz), 3·75 (2H, m), 3·13 (1H, q, $J = 6$ Hz), 2·2 (2H, brm), 1·41 (3H, d, $J = 6$ Hz). V_{max} 3420, 2970, 1580, 1549, 1499, 1465 cm^{-1}.

In a similar manner:

Cis-*and* trans-*1-pyrimidin-2-yl-2-methyl-3-phenylpyrrolidine* **54** and **55** were prepared from **50** and 2-chloropyrimidine.

Cis-*isomer:* **54**, δ_H ($CDCl_3$ 500 MHz) 8·32 (2H, d, $J = 4{\cdot}5$ Hz), 7·34 (3H, m), 7·25 (2H, m), 6·45 (1H, d, $J = 4{\cdot}5$ Hz), 4·60 (1H, quin. $J = 7$ Hz), 3·84 (1H, m), 3·63 (2H, m) 2·50 (1H, m), 2·27 (1H, m), 0·88 (3H, d, $J = 6$ Hz). V_{max} 3100, 2970, 2400, 1580, 1550, 1500, 1340 cm^{-1}.

Trans-*isomer:* **55**, δ_H ($CDCl_3$) 500 MHz), 8·33 (2H, d, $J = 4{\cdot}5$ Hz), 7·3 (3H, m), 7·23 (2H, m), 6·48 (1H, t, $J = 4{\cdot}5$ Hz), 4·32 (1H, m), 3·92 (1H, m), 3·67 (1H, m), 3·16 (1H, m), 2·44 (1H, m), 2·05 (1H, m), 1·42 (3H, d, $J = 6$ Hz). V_{max} 3100, 2770, 2400, 1580, 1550, 1335 cm^{-1}.

Cis-*and* trans-*1-(4,6-dimethyl pyrimidin-2-yl)-2-methyl-3-(4*-tert-*butylphenyl)pyrrolidine* **56** and **57** were prepared from **45** and 2-chloro-3,5-dimethylpyrimidine.

Cis-*isomer:* **56**, δ_H (90 MHz) 7·30 (4H, m), 6·28 (1H, s), 4·70 (1H, m), 3·5–4·0 (3H, m), 2·2–2·5 (2H, m), 2·3 (6H, s), 1·3 (9H, s), 0·90 (3H, D, $J = 6$ Hz).

Trans-*isomer:* **57**, δ_H (90 MHz) 7·30 (4H, m), 6·28 (1H, s), 4·27 (1H, m), 3·5–4·1 (2H, m), 3·15 (1H, m), 2·3 (6H, s), 1·85–2·5 (2H, m), 1·35 (12H, m). V_{max} 3270, 3035, 2933, 2861, 1646, 1490 cm^{-1}.

Cis *and* trans *1-(pyrimidin-2-yl)-2-methyl-3-octylpyrrolidine* **58** and **59** were prepared from **53** and 2-chloropyrimidine.

Cis-*isomer:* **58**, δ_H (90 MHz) ($CDCl_3$) 8·40 (2H, d, $J = 4{\cdot}5$ Hz), 6·47 (1H, t, $J = 4{\cdot}5$ Hz), 4·35 (1H, m), 3·60 (2H, m), 2·05 (3H, m), 1·35 (14H, m), 1·1 (3H, d, $J = 7$ Hz), 0·9 (3H, m).

Trans-*isomer:* **59**, δ_H (90 MHz) 8·28 (2H, d, $J = 5$ Hz), 6·42 (1H, t, $J = 5$ Hz), 3·4–4·3 (3H, m), 1·9 (2H, m), 1·3 (17H, m), 0·9 (1H, m).

1-pyrimidin-2-yl-pyrrolidine, **60** was prepared from pyrrolidine and 2-chlorpyrimidine. δ_H (90 MHz) 8·37 (2H, d, $J = 4{\cdot}5$ Hz), 6·50 (1H, t, $J = 4{\cdot}5$ Hz), 3·60 (4H, m) 2·0 (4H, m). V_{max} 2950, 2870, 1590, 1560, 1520, 1390, 1340 cm^{-1}.

Cis-N-(*tetrahydropyrimidin-2-yl*)-*2-methyl-3-*(*4*-tert-*butylphenyl*)*pyrrolidinium acetate*, ***10***

Cis-pyrimidinylamine **45** (540 mg) was dissolved in ethanol (20 ml) containing 10% Pd/C (100 mg) and acetic acid (0·5 ml) added. The mixture was hydrogenated at room temperature and pressure with shaking for 8 h until the theoretical quantity of hydrogen had been absorbed. The mixture was passed through celite and the filtrate evaporated under reduced pressure. A gum **10** (0·5 g) was collected. δ_H (90 MHz) 9·1 (2H, NHs), 7·22 (4H, ABq, $J = 8$ Hz), 4·6 (1H, m), 3·84 (2H, m), 3·34 (4H, m), 2·26 (2H, m), 1·93 (3H, s), 1·90 (2H, m), 1·25 (9H, s), 0·80 (3H, d). V_{max} 3180, 2980, 1640, 1583, 1450, 1400 cm^{-1}.

In a similar manner:

Trans-N-(*tetrahydropyrimidin-2-yl*)-*2-methyl-3-*(*4*-tert-*butylphenyl*)*pyrrolidinium acetate*, **9**, was prepared from **46**. δ_H (90 MHz) 9·35 (2H, m), 7·21 (4H, ABq, $J = 8$ Hz), 4·26 (1H, m) 3·63 (2H, m) 3·32 (4H, m), 2·96 (1H, m), 2·16 (2H, m), 1·82 (3H, s), 1·80 (2H, m), 1·30 (9H, s), 1·25 (3H, d). V_{max} 3180, 2980, 1640, 1583, 1450, 1400 cm^{-1}.

Cis-N-(*tetrahydropyrimidin-2-yl*)-*2-methyl-3-*(*4*-tert-*butylphenyl*)*pyrrolidinium chloride* **61** was prepared from **45**. δ_H (250 MHz) 8·1 (2H, brs), 7·29 (2H, d, $J = 8$ Hz) 7·12 (2H, d, $J = 8$ Hz), 4·73 (1H, m), 3·95 (1H, m), 3·5–3·7 (2H, m), 3·4 (4H, m), 2·2–2·4 (2H, m), 1·83 (1H, m) 1·275 (9H, s), 0·835 (3H, d, $J = 6$ Hz). MS (FAB Ionisation) 300(M^+), 112.

Trans-N-(*tetrahydropyrimidin-2-yl*)-*2-methyl-3-*(*4*-tert-*butylphenyl*)*pyrrolidinium chloride*, **12** was prepared from **46**. δ_H (90 MHz) 7·35 (2H, m), 7·3 (4H, m), 4·2 (1H, m), 3·5 (4H, m), 3·05 (2H, m), 2·15 (1H, m), 1·8 (4H, m), 1·3 (12H, m).

Cis-N-(*tetrahydropyrimidin-2-yl*)-*2-methyl-3-phenyl pyrrolidinium acetate*, **8** was prepared from **54**. δ_H (90 MHz) ($CDCl_3/D_2O$), 7·22 (5H, m), 4·58 (1H, m), 3·5–4·0 (3H, m), 3·37 (4H, m), 2·0–2·6 (2H, m), 1·98 (3H, s), 1·85 (2H, m), 0·75 (3H, d,$J = 6$ Hz). V_{max} 3300, 3200, 2970, 2900, 1640, 1575, 1320 cm^{-1}.

Trans-N-(*tetrahydropyrimidin-2-yl*)-*2-methyl-3-phenyl-pyrrolidinium acetate* **7** was prepared from **55**. δ_H (90 MHz) ($CDCl_3$) 9·2 (2H, m), 7·2 (5H, m), 4·27 (1H, m), 3·60 (2H, m), 2·95 (1H, m), 2·0–2·4 (2H, m), 1·84 (3H, s), 1·75 (2H, m), 1·25 (3H, d, $J = 6$ Hz). V_{max} 3400, 3300, 3200, 2970, 2900, 1640, 1575, 1430, 1320 cm^{-1}.

Cis - N - (*4,6 - dimethyltetrahydropyrimidin - 2 - yl*) - *2 - methyl-3-*(*4*-tert-*butylphenyl*)*pyrrolidinium chloride*, **13** was prepared from **56**. δ_H (250 MHz) 7·66 (1H, brs), 7·315 (2H, d, $J = 8$ Hz), 7·16 (2H, d, $J = 8$ Hz), 7·07 (1H, brs), 5·00 (1H, m), 4·06 (1H, m), 3·5–3·8 (4H, m), 2·2–2·5 (2H, m), 2·00 (1H, m), 1·9 (1H, brm), 1·45 (3H, d, $J = 6$ Hz), 1·43 (3H, d, $J = 6$ Hz), 1·28 (9H, s), 0·82 (3H, d, $J = 6$ Hz). V_{max} 3420, 3230, 2980, 1640, 1580, 1470 cm^{-1}. MS (FAB) 328 (M^+).

Trans - *N* - (*4,6 - dimethyltetrahydropyrimidin - 2 - yl*) - *2 - methyl-3-*(*4*-tert-*butylphenyl*)*pyrrolidinium chloride*, **14** was prepared from **57**. V_{max} 3180, 3060, 2980, 1630, 1576 cm^{-1}.

Cis-N-*tetrahydropyrimidin-2-yl*)-*2-methyl-3-octylpyrrolidinium chloride*, **62** was prepared from **58**. δ_H (250 MHz) 8·02 (2H, brs), 4·38 (1H, m), 3·76 (1H, m) 3·58 (1H, m), 3·42 (4H, m), 2·05 (2H, m), 1·87 (2H, m), 1·63 (1H, m), 1·25 (15H, m), 1·03 (3H, d, $J = 6$ Hz), 0·88 (3H, t). V_{max} 3400, 3180, 3070, 2935, 1660, 1600 cm^{-1}. MS (FAB) 280 (M^+).

Trans-N-(*tetrahydropyrimidin-2-yl*)-*2-methyl-3-octylpyrrolidinium chloride*, **15** was prepared from **59**. δ_H (250 MHz), 7·89 (2H, brs), 3·95 (1H, m), 3·5–3·8 (2H, m), 1·89 (2H, m), 1·63 (1H, m), 1·25 (18H, m), 0·88 (3H, t). MS (FAB) 280 (M^+).

1-(Hexahydropyrimidin-2-yl)pyrrolidinium acetate, **11** was prepared from **60**. δ_H (90 MHz) 8·8 (2H, brs), 3·45 (8H, m) 1·9 (3H, s), 1·85 (6H, m).

N-(*1-(4-tert-Butylphenyl)prop-2-yl*)-N′-*phenylacetamidine hydrochloride*, ***17***.

N-(1-(4-*tert*-Butylphenyl prop-2-yl) acetamide **47 R = Me**, (2·1 g, 8·5 mmol) and aniline (2·44 g, 26·2 mmol) were dissolved in dry chloroform (50 ml) and the mixture cooled to 0°C and stirred under nitrogen. Phosphorus pentachloride (2·48 g, 11·80 mmol) was added and the mixture allowed to warm to room temperature. An exotherm was noticed. The mixture was then heated under reflux for 1 h. Water (30 ml) was added to the cooled mixture and the whole stirred vigorously for 30 min. The aqueous layer was separated and the organic layer washed with water until the washings had a pH of greater than 4. The organic layer was dried and concentrated. The residue was triturated with ethyl methyl ketone and the resulting colourless solid collected. This was recrystallised from ethyl methyl ketone. Yield 1·4 g (45%), m.p. 212·9°C (corrected); δ_H ($CDCl_3$) 11·62 (1H, brs), 10·76 (1H, brd, J = 9·6 Hz), 7·37 (2H, d, J = 8 Hz), 7·2 (4H, m), 6·83 (1H, brs), 6·74 (1H, d, J = 8 Hz), 3·73 (1H, m), 2·92 (2H, m), 2·31 (3H, s), 1·5 (3H, d, J = 6·5 Hz), 1·34 (3H, s), 1·32 (9H, s) δ_C 13·3, 21·1, 31·3, 34·4, 43·5, 53·8, 123·1, 125·6, 126·6, 129·0, 129·2, 129·6, 134·5, 134·7, 139·8, 150·2, 165·4. V_{max} 3429, 2971, 2881, 1653, 1595, 1497 cm^{-1}.

N-(*1-(4-tert-Butyl phenyl)prop-2-yl*)-N′-*phenylacetamidine* ***63***.

A sample of **17** was dissolved in water and basified with 2 M sodium hydroxide. The mixture was extracted with ether, the organic layer washed once with water, dried and concentrated to afford a gummy residue in quantitative yield. δ_H ($CDCl_3$) 7·25 (5H, m), 6·97 (1H, m), 6·73 (2H, d, J = 8 Hz), 4·35 (1H, m), 2·85 (2H, m), 1·7 (3H, s), 1·33 (9H, s), 1·2 (3H, d, J = 7 Hz); δ_C 7·6, 20·0, 31·4, 34·4, 41·5, 46·6, 121·6, 122·2, 125·1, 128·6, 129·3, 135·4, 148·9, 151·9, 154·2. V_{max} 3275, 2967, 1634, 1595, 1490, 1231 cm^{-1}.

In a similar manner:

N-(*1-(4-tert-butylphenyl)-prop-2-yl*)-N′-*phenylformamidine hydrochloride* **16** was prepared from **47 R = H** and aniline. Yield 75% (as a gum). δ_H ($CDCl_3$) 12·1 (1H, d, J = 12 Hz), 10·65 (1H, dd, J = 12·9 Hz), 7·25 (8H, m), 6·8 (2H, d, J = 8 Hz), 2·95 (1H, dd, J = 5 Hz), 2·84 (1H, dd, J = 8 Hz), 1·5 (3H, d, J = 7 Hz), 1·25 (9H, s), δ_C 20·4, 13·3, 34·5, 43·4, 57·6, 118·7, 126·0, 126·8, 129·2, 129·7, 129·8, 133·6, 150·4, 152. V_{max} 3177, 2968, 1695, 1603, 1501, 1353 cm^{-1}.

N-(*1-(4-tert-Butylphenyl)prop-2-yl*)-N′-*phenylformamidine*, **64** was prepared from **16**. δ_H 7·3 (8H, m), 7·0 (1H, m), 6·85 (1H, brs), 2·8 (3H, m), 1·3 (9H, s), 1·26 (3H, d, J = 7 Hz). V_{max} 3213, 2968, 1667, 1641, 1593, 1490, 1192 cm^{-1}.

N-(*1-(4-tert-Butylphenyl)prop-2-yl*)-N′-(*4-methylphenyl*)*acetamidine hydrochloride* **26** was prepared from **47 R = Me** and 4-methylaniline. Yield 40% as a colourless solid recrystallised from ethyl methyl ketone, m.p. (corrected) 167·4°C. δ_H ($CDCl_3$) 11·46 (1H, brs), 10·74 (1H, brd, J = 9 Hz), 7·38 (2H, d, J = 10 Hz), 7·25 (2H, d, J = 10 Hz), 7·12 (2H, d, J = 8 Hz), 6·84 (2H, d, J = 8 Hz), 3·73 (1H, m), 2·91 (2H, m), 2·33 (3H, s), 1·48 (3H, d, J = 6·5 Hz), 1·32 (9H, s), 1·28 (3H, s); δ_C 13·5, 21·1, 31·4, 34·5, 43·6, 53·9, 125·7, 126·1, 129·7, 130·1, 132·2, 134·6, 138·6, 150·3, 165·7. V_{max} 3427, 3196, 2967, 1650, 1614, 1582, 1519, 1434 cm^{-1}.

N-(*1-(4-tert-Butylphenyl)prop-2-yl*)-N′-(*3-methylphenyl*)*acetamidine hydrochloride* **25** was prepared from **47 R = Me** and 3-methylaniline. Yield 16% as a colourless solid recrystallised from ethyl methyl ketone, m.p. (corrected) 192·9°C. δ_H 11·62 (1H, brs), 10·76 (1H, brd, J = 9·6 Hz), 7·37 (2H, d, J = 8 Hz), 7·2 (4H, m), 6·83 (1H, brs), 6·74 (1H, d, J = 8 Hz), 3·73 (1H, m), 2·92 (2H, m), 2·31 (3H, s), 1·51 (3H, d, J = 6·5 Hz); δ_C 13·3, 21, 31·3, 34·4, 43·5, 53·8, 123·1, 125·6, 126·6, 129·0, 129·2, 129·6, 134·5, 134·7, 139·8, 150·2, 165·4. V_{max} 3429, 3188, 2966, 1647, 1609, 1591, 1515, 1491, 1431 cm^{-1}.

N-(*1-(4-tert-Butylphenyl)prop-2-yl*)-N′-(*2-methylphenyl*)*acetamidine hydrochloride* **24** was prepared from **47 R = Me** and 2-methylaniline. Yield 32% as a colourless solid recrystallised from ethyl methyl ketone, m.p. (corrected) 191·8°C. δ_H 11·46 (1H, brs), 10·74 (1H, d, J = 9·6 Hz), 7·39 (2H, m), 7·25 (2H, m), 7·1 (2H, d, J = 8 Hz), 6·84 (2H, d, J = 8 Hz), 3·73 (1H, m), 2·95 (2H, m), 2·33 (3H, s), 1·45 (3H, d, J = 6 Hz), 1·32 (9H, s), 1·28 (3H, s). V_{max} 3428, 3191, 2968, 1651, 1614, 1582, 1519, 1434, 1383 cm^{-1}.

N-(*1-(4-tert-Butylphenyl)prop-2-yl*)-N′-(*4-chlorophenyl*)*acetamidine hydrochloride* **28** was prepared from **47 R = Me** and 4-chloroaniline. Yield 90% as colourless needles from ethanol/ethyl methyl ketone, m.p. (corrected) 234·8°C. δ_H 11·65 (1H, s), 10·70 (1H, d, J = 10 Hz), 7·3 (6H, m), 7·93 (2H, d, J = 8 Hz), 3·75 (1H, m), 2·9 (2H, m), 1·5 (3H, d, J = 6 Hz), 1·35 (3H, s), 1·32 (9H, s); δ_C 12·6, 21·1, 31·5, 34·4, 43·5, 54·1, 125·8, 128·9, 129·7, 133·3–134·9, 149·3, 161·9. V_{max} 3426, 3190, 2967, 1647, 1593, 1515, 1496, 1459, 1432 cm^{-1}.

N-*1-(4-tert-Butylphenyl)prop-2-yl*)-N′-(*3-chlorophenyl*)*acetamidine hydrochloride* **27** was prepared from **47 R = Me** and 3-chloroaniline. Yield 50% as a colourless solid from methanol/ethyl methyl ketone, m.p.

(corrected) 217·8°C. δ_H 11·95 (1H, brs), 10·89 (1H, brd, $J = 9{\cdot}9$ Hz), 7·39 (2H, d, $J = 8$ Hz), 7·27 (4H, m), 7·0 (1H, brs), 6·9 (1H, m), 3·72 (1H, m), 2·92 (2H, m), 1·53 (3H, d, $J = 6{\cdot}5$ Hz), 1·32 (9H, s); δ_C 13·4, 21·0, 31·3, 43·5, 54·1, 124·3, 125·7, 126·3, 128·5, 128·5, 129·6, 130·5, 134·3, 135·1, 151, 165·4. V_{max} 3426, 3194, 2969, 1647, 1594, 1513, 1479, 1434 cm^{-1}.

N-(*1*-(*4*-tert-*Butylphenyl*)*prop-2-yl*)-N′-(*3,4-dichlorophenyl*)*acetamidine hydrochloride* **29** was prepared from **47 R = Me** and 3,4-dichloroaniline. Yield 38% as a colourless solid from methanol/ethyl methyl ketone, m.p. (corrected) 214·8°C. δ_H 10·9 (1H, brd, $J = 9{\cdot}6$ Hz), 7·4 (3H, m), 7·25 (2H, d, $J = 8$ Hz), 7·11 (1H, d, $J = 2{\cdot}4$ Hz), 6·86 (1H, dd, $J = 8{\cdot}5$, 2·4 Hz), 3·75 (1H, m), 2·93 (2H, m), 1·54 (3H, d, $J = 6{\cdot}4$ Hz), 1·33 (12H, s). V_{max} 3428, 2968, 1650, 1591, 1568, 1517, 1475, 1430 cm^{-1}.

N-(*1*-(*4*-tert-*Butylphenyl*)*prop-2-yl*)-N′-(*4-methoxyphenyl*)*acetamidine hydrochloride* **23** was prepared from **47 R = Me** and 4-methoxyaniline. Yield 93% as a colourless powder from ethyl methyl ketone, m.p. (corrected) 188·6°C. δ_H 11·4 (1H, s), 10·78 (1H, d, $J = 9{\cdot}6$ Hz), 7·37 (2H, d, $J = 8$ Hz), 7·25 (2H, d, $J = 8$ Hz), 6·9 (2H, d, $J = 8$ Hz), 6·81 (2H, d, $J = 8$ Hz), 3·79 (3H, s), 3·72 (1H, m), 2·92 (2H, m), 1·5 (3H, d, $J = 6{\cdot}5$ Hz), 1·3 (9H, s), 1·29 (3H, s); δ_C 13·3, 21·0, 31·3, 34·4, 43·5, 53·8, 55·4, 114·6, 125·6, 127·7, 129·6, 134·5, 150·2, 159·3, 165·8. V_{max} 3428, 2968, 1649, 1613, 1581, 1518, 1433 cm^{-1}.

N-(*1*-(*4*-tert-*Butylphenyl*)*prop-2-yl*)-N′-(*3-methoxyphenyl*)*acetamidine hydrochloride* **22** was prepared from **47 R = Me** and 3-methoxyaniline. Yield 43% as a colourless powder after column chromatography (silica gel, chloroform + methanol) and recrystallisation from ethyl methyl ketone, m.p. 188·5°C. δ_H ($CDCl_3$) 10·81 (1H, d, $J = 9{\cdot}5$ Hz), 7·38 (2H, d, $J = 8$ Hz), 7·32 (1H, 6·5), 7·25 (3H, m), 6·83 (4H, dd, $J = 2{\cdot}8$ Hz), 6·54 (2H, m), 3·77 (3H, s), 3·75 (1H, m), 2·9 (2H, m), 1·52 (3H, d, $J = 6$ Hz), 1·37 (3H, s), 1·31 (9H, s).

N-(*1*-(*4*-tert-*Butylphenyl*)*prop-2-yl*)-N′-(*2-methoxyphenyl*)*acetamidine hydrochloride* **21** was prepared from **47 R = Me** and 2-methoxyaniline. Yield 52% as a colourless powder from ethyl methyl ketone after column chromatography (silica, chloroform + methanol), m.p. (corrected) 164·5°C. δ_H ($CDCl_3$) 11·08 (1H, brs), 10·97 (1H, d), 7·3 (5H, m), 6·93 (3H, m), 3·80 (3H, s), 3·73 (1H, m), 2·93 (2H, d, $J = 7$ Hz), 1·39 (3H, s), 1·30 (9H, s); δ_C 13·1, 21·0, 31·3, 34·4, 43·3, 53·8, 55·8, 111·9, 120·7, 123·6, 125·5, 127·9, 129·4, 129·8, 134·5, 150, 154, 166.

N-(*1*-(*4*-tert-*Butylphenyl*)*prop-2-yl*)-N′-(*4-hydroxyphenyl*)*acetamidine hydrochloride* ***20***.
Compound **23** (2·5 g, 6·67 mmol) in dry dichloromethane (40 ml) was cooled to − 78°C. A solution of boron tribromide in dichloromethane (1 M; 13 ml, 13·3 mmol) was added dropwise to the stirred solution. The mixture was allowed to warm to room temperature and was left for 48 h. The mixture was diluted with dichloromethane and poured into saturated sodium hydrogen carbonate solution. The organic layer was separated and the precipitaginous aqueous layer extracted twice with dichloromethane. The organic extracts were combined and washed twice with water. They were then dried over sodium sulfate, filtered and the solvent removed under vacuum to afford a gum. This was triturated with ethyl methyl ketone + hexane to afford a colourless crystalline solid which was collected and recrystallised from ethyl methyl ketone. Yield 40%, m.p. (corrected) 235·2°C. δ_H ($CDCl_3$, NaOD), 7·295 (2H, d, $J = 8$ Hz), 7·09 (2H, brd, $J = 8$ Hz), 6·67 (2H, d, $J = 8$ Hz), 6·55 (2H, d, $J = 8$ Hz), 4·55 (1H, m), 2·75 (2H, m), 1·75 (3H, brs), 1·31 (9H, s), 1·15 (3H, d, $J = 6$ Hz); δ_C 17, 20·9, 31·4, 34·4, 42·6, 49, 116·4, 124·2, 125·3, 129·2, 134·8, 149·4, 153, 158, 163.

In a similar manner:

N-(*1*-(*4*-tert-*Butylphenyl*)*prop-2-yl*)-N′-(*3-hydroxyphenyl*)*acetamidine hydrochloride* **19** was prepared from **22**. Yield 73% as a colourless powder from methanol + ethyl methyl ketone, m.p. (corrected) 253·4°C.

N-(*1*-(*4*-tert-*Butylphenyl*)*prop-2-yl*)-N′-(*2-hydroxyphenyl*)*acetamidine hydrochloride* **18** was prepared from **21**. Yield 63% as a colourless powder from methanol + ethyl methyl ketone, m.p. (corrected) 213·0°C.